The vestibulo-ocular reflex (VOR) during high-frequency head rotation

Chapter

7

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

The aim of this study was quantification of the Vestibulo-Ocular Reflex (VOR) during high-frequency horizontal head rotation by use of Electro-Oculography (EOG). Our experiments were started in normal subjects using active head rotation measuring head velocity by an angular rate sensor mounted on a headband as has previously been described by O'Leary et al.[1,2] Using a headband fixed rate sensor we found a decreasing gain and an increasing phaselag with increased rotation frequency in contrast to O'Leary et al. and Tomlinson et al.[1,2,3] This difference possibly can be attributed to a difference in analysing technique or registration technique of head velocity. The experiment using a biteboard fixed rate sensor indeed showed that gain and phase are close to 1.0 and 0° respectively over the whole frequency range between 2 and 6 Hz. The difference is probably explained by slippage of the headband relative to the head at the higher frequencies. Conclusion: head velocity is detected more accurately with the biteboard fixed sensor and experiments were continued by using this application.

It appeared that 60% of the subjects in the headband group and 38 % of the subjects in the biteboard group, did not show active head rotation frequencies exceeding 4.5 Hz despite intensive instructions. The difference might be due to the fact that the headband is less comfortable and slips along the head compared to the steady fixed biteboard and as mentioned above, does not sense real head velocity. This explanation was confirmed by the subjective sensations of the subjects. However, in the study of O'Leary et al. and Tomlinson et al. *all* subjects reached a frequency of 6 Hz.[1,2,3] The study of O'Leary et al. of age-related responses of the VOR shows that head movements in some subjects of the elderly population were generally slower (less than 4 Hz).[4] We could not confirm that the majority of normal subjects were able to reach active head rotation frequencies up to 6 Hz. Apart from differences with respect to training and subjects it might be that the frequency analyses differ to some extent. Contribution of higher harmonics and non-linearities introduce a major problem analysing the responses. If a person is asked to rotate the head at 6 Hz, but only reaches 3 Hz, spectral analysis will show a substantial head and eye velocity at 3, 6, 12, 24 Hz etc. Also, head velocity especially at higher frequencies is not sinusoidal perse and contain lower and higher non-harmonic components. In this example using our analysis, the response is only attributed to the maximum amplitude in the head velocity spectrum (3 Hz) and therefore shows no response at 6 Hz. According to our interpretation of the data-analysis performed by O'Leary et al., the second harmonics of the 3 Hz component might have attributed to the 6 Hz response etc. and enhance the high-frequency VOR gain artificially.[1,2,4]

The aspect of reaching a limited frequency range in case of active head rotation ha been overcome by Tabak et al. by using a computer driven headshaker which ca rotate the head passively up to 20 Hz.[5,6] Eye and head movements in their study wer recorded using the scleral coil technique (SCT) and VOR responses to sinusoidal hea movements were analyzed. From 2 Hz on they found an initial gain of 1, whic steadily decreased with a minimum of approximately 0.8 at 8 Hz, and subsequentl increased to 1.1-1.3 at 20 Hz. Phaselag increased from about zero to about 45° at 2 Hz. According to their idea we developed a passive head rotation test and in an effor to determine whether the VOR differed during active versus passive head rotation a direct comparison was made in a group of normal subjects (Chapter 3). Analysis of th VOR between 2-6 Hz using EOG resulted in approximately similar findings a compared with the scleral coil technique mentioned above. This might enable an facilitate a broad clinical application of high-frequency testing, because EOG is les invasive and easier to use in the clinic compared to the SCT. Above 5-6 Hz however the amplitude of the induced eye velocities is too small to be detected accurately wit EOG.

The advantage of the passive test versus the active head rotation test was that during passive testing head movement was approximately sinusoidal, whereas during active head rotation head velocity showed many non-sinusoidal components. As a consequence the analysis was more precise and easier using passive head rotation.

It appeared in this study that during passive rotation, by means of a computer-driven headshaker, if responding properly to the stimulus, all subjects were able to reach rotation frequencies of 6 Hz. However, some (about 5%) subjects were unable to relax their neck muscles, which lead to an inefficient transfer of the stimulus upon the head. These subjects were excluded from further analysis. Upon active and passive isolated head rotation the VOR was found to be fairly optimal between 2-4 Hz with an almost constant gain of one and approximately no phaseshift. Above 4 Hz active head rotation resulted in a more optimal reflex as compared to passive rotation: during passive head rotation gain decreased to 0.82 at 6 Hz in agreement with Tabak et al.[5,6] Collewijn et al. studied the VOR in active versus passive head rotation in low frequencies up to 1.33 Hz, using the SCT for detection of eye position.[7] They found gain values being 3% lower during passive compared to active rotation in the light and 13% in the dark. Goebel et al. also studied the VOR during passive and active head rotation in low frequencies up to 1 Hz, using EOG for eye movement detection.[8] At 1 Hz no difference in gain (approximately 0.90) during active and passive head rotation was found.

Anticipation might be a mechanism for a better VOR during active compared to passive head rotation. The eye movement strategy may contain a central motor programme, that optimises the VOR through the predictability of the target or movements and prior knowledge or experience with the task.[9,10,11,12,13,14,15] The finding that there is a difference between active and passive head rotation above 4 Hz might point

to a substantial contribution of such a central motor programme to the VOR above 4 Hz.

Comparison of our data of passive high-frequency head rotation with high-frequency whole body rotation introduces some interpretation difficulties. Theoretically there is a difference between head and whole body rotation. In case of whole body rotation no cervical input to the vestibular system is achieved. The Cervico-Ocular Reflex (COR) is supposed to cause eye deviations in the opposite direction of body rotation in the absence of visual or vestibular stimulation.[16,17] The COR, although virtually non-existent in normal animals, has been shown in labyrinthine-defective animals to become increasingly instrumental in restoring the slow compensatory eye movements which accompany head movements.[18,19,20] For example, it was shown that in normal monkeys the COR contributes little (2-3%) to ocular stabilisation during rapid head movements. However, in the labyrinthectomised monkeys, the contribution of the passively induced COR to gaze stability increases to about 30%, while during active movements it apparently reaches values near 80%.[19] In literature a large variability in human COR gains is reported, not only among normal subjects but also in patients with bilateral vestibular loss; the results are controversial.[21,22,23] Several studies report a COR enhancement in patients with bilateral vestibular impairment.[22,24,25,26] However it was also found, that the COR was best elicited during low-frequency stimulation[16,24], low stimulus velocities[27], active head movements[26] and with eyes closed[6,22] . Thoden et al. found that the COR could be enhanced by the instruction to imagine head movement.[28] Besides, the COR, involving a multisynaptic pathway, has a latency of about 100 msec which makes it unlikely that the COR is functional at high stimulus frequencies.[29] We assume that the COR does not substantially contribute to the VOR found at high-frequency passive head rotation in normal subjects. It is possible, that in patients with bilateral vestibular impairment, the COR contributes somewhat to the ocular responses we detected, especially at the lower frequencies. Huygen et al. investigating 30 patients, found that the COR-gain was frequency dependent, decreasing from 0,7 at 0,1 Hz to 0,4 at 0,4 Hz.[24] Therefore it is unlikely that the COR contributes to a great extent to the ocular responses found in patients with bilateral vestibular impairment at the higher frequencies.

At high-frequency whole body rotation also other diffuse tactile, proprioceptive information reaches the brainstem which contributes to the perception of movement of the body or body components and may affect the VOR gain and phase. All these aspects point to a possible difference in data to be found when comparing whole body versus isolated head rotation. Some studies report an increase in gain up to 4 in higher frequencies. Keller and Benson studying monkeys and humans respectively during passive whole body rotation, found horizontal gain rising to 1.4 and 2 at 4 and 5 Hz respectively.[30,31] In these studies however, eye velocity was compared to chair velocity

instead of head velocity and during whole body rotation at high frequencies heac trunk and chair movements may differ considerably due to poor fixation of the variou body components. This might be the reason, that gain was somewhat overestimate sometimes, which was confirmed in a study by Larsby et al.[32] Hoshowski et al however, measured gain during passive high-frequency whole body rotation with a angular rate sensor attached to a headband, thus comparing eye velocity to hea instead of chair velocity.[33] He found an increase in gain, 1.0 at 2 Hz increasing up t 1.7 at 4 Hz. However, in this study the inaccuracies of the headband fixed senso described previously might exist. Analysis of the data in literature suggests that th peak velocity of the stimulus (body or head velocity) does not affect the VOR gain to a large extent in the velocity range applied. So a difference in peak velocity could no explain the differences in gain of the VOR measured upon head or whole body rotation. Tabak et al. recently confirmed that even in isolated head rotation the VOR gain indeed slightly increases up to 1.3 at 20 Hz, although the gain started to increase only beyond 8 Hz .[5,6] This effect is not large, but indicates that the difference between VOR gain between isolated head and whole body rotation needs further research.

Dayal & Tomlinson using pseudorandom whole body rotation of 2-5 Hz comparing normal subjects and patients with *Meniere's disease*, found that patients showed a gain exceeding normal values in the higher frequency range.[34] This increased gain was attributed to the acceleration sensitivity of the lateral semicircular canal afferents at high frequencies in patients. Phase values were not discussed. As discussed above these results should be interpreted with caution because inaccuracies in body and head fixation as well as head velocity detection often occurs in case of high-frequency whole body rotation.[35]

An increasing phaselag of the VOR at higher frequencies was suggested to be a useful diagnostic indicator for Meniere's disease by Matthew et al. using the *active* Vestibular Autorotation Test (VAT).[36] Although no difference was found between normal subjects and Meniere's disease patients in the acute stage of the disease; in the chronic stage of the disease decreased gain and increased phaselags at higher frequencies were found. At 5 and 6 Hz 85% of the patients were found to have abnormal gain or phase values regardless the clinical stage. However, it must be stressed that Matthew et al.defined the normal range by the average ± 1 SD, which is a rather soft criterium.[26] If the more accepted criterium of ± 2 SD is applied less than 50% of the patients show abnormal values. The results of Matthew et al. show a tendency that the high-frequency VOR deteriorates in the chronic stage of the disease.[26] Quantification of low- (calorics) and high- (head rotation) frequency testing in a longitudinal study of Meniere's disease patients might inform us about the relation between test outcome and stage or severity of the disease.

O'Leary & Davis reported an increased velocity gain at high frequencies during the

vertical VAT (2-6 Hz) in 10 patients in the acute stage of Meniere's disease.[2] We were unable to reproduce their results, because in a pilot study performed in normal subjects it appeared impossible to detect eye movements accurately due to the poor linearity and reliability of the vertical leads applying EOG. Besides, it appeared to be even more difficult to reach high rotation frequencies during vertical rotation compared to horizontal rotation, and more eye blinking artefacts occurred. In summary: there is no conclusive evidence that the VOR at high-frequency *active* horizontal *head* rotation is affected in Meniere's disease patients.

One might hypothise that in Meniere's disease anticipation and a central motor programme might compensate for vestibular loss at higher frequencies which might result in a good gain and phase during active head rotation and that the function loss can only be detected by use of non-voluntary stimuli. The observation that unpredictable high-velocity impulses are also useful in detection of 'low-frequency compensated' vestibular lesions supports this interpretation.[5,6,37] Another hypothesis could be, that the COR contributes to the responses found, although in the higher frequencies applied this is unlikely.

To investigate whether the passive high-frequency head rotation test was able to distinguish between Meniere's disease patients and normal subjects, we studied 20 *patients with Meniere's disease* classified according to the AAO-HNS criteria (Chapter 4).[38] The gain of the VOR between 2-6 Hz and the phaselag between 2-3 Hz, showed to be almost similar in Meniere's disease patients compared to normal subjects. Above 3 Hz the phaselag in patients using passive head rotation was significant larger than in normal subjects. At 3 and 4 Hz the difference between normal subjects and patients is maximum, as above 4 Hz the accuracy of the measurements decreased too much to allow a reliable discrimination (see above). However, four patients, clinically defined as having Meniere's disease according to the AAO-HNS criteria, with normal calorics and a normal low-frequency VOR, had abnormal phase values during passive head rotation, which is suggestive for the relevance of evaluating the high-frequency VOR.

Vestibular tests using high-frequency head rotation in patients with *bilateral vestibular impairment* has not been performed to a great extent yet. Goebel & Rowdon studied 34 subjects with bilateral reduced caloric responses using active head rotation and whole body rotation, both at 0.5 Hz.[39] Roughly one third showed a decreased VOR gain compared to normal subjects in both circumstances. Hydén et al. studied the VOR during high-frequency whole body rotation.[40] At high frequencies (>3 Hz) all patients showed reduced VOR gains compared to normal subjects. At low-frequencies gain values were close to normal when using a predictable stimulus (sinusoidal). With a non-predictable (pseudorandom) stimulation gain values were significantly reduced even at lower frequencies. Patients with the most severe loss showed a phaselag at higher frequencies. It must be mentioned that gains were found to increase at higher

frequencies, which might be due to errors made in detecting head velocity as discusse above.

Tabak et al. studied 3 patients with bilateral vestibular impairment using passive higl frequency head rotation.[5,6] Eye position was detected by the SCT. Values of the VO gain of these patients were clearly lower and phaselags larger, compared to norm subjects in the 2-8 frequency range. The patient who had only mild vestibular sym toms in daily life, showed better VOR gain and phase values. This might indicate th high-frequency VOR characteristics correlate with compensation and clinical recove after bilateral vestibular impairment.

We studied patients with *bilateral vestibular caloric hyporeflexia* using passive higl frequency head rotation (Chapter 5). It was observed that absence of the VOR durin low-frequency whole body rotation did not imply absence of the VOR at higl frequency passive head rotation. Patients with an absent VOR during low-frequenc rotation had a tendency to show lower gains at higher frequencies as compared t patients with a normal low-frequency VOR.

After bilateral vestibular function loss, most patients return to near normal lifestyl but when high-skilled locomotor performances are demanded, man can not completel compensate for total vestibular loss. Most labyrinthine defective individuals experier ce imbalance and oscillopsia, which is a disturbing illusion of movement of th environment while walking or in other ways while moving the head rapidly.[41,42] Thi transient blurring of vision during rapid head movements is a very common, but nc compulsatory finding, as was also reported by patients in this study.[43] One woul expect that patients who experience oscillopsia would have more difficulty performin in high-frequency rotation tests. This could not be confirmed in this study, mayb because some patients find it very difficult to describe their specific sensations. A fe patients reported persistent distressing postural unsteadiness or oscillopsia. Here vestibular compensation may have failed to occur, may be incomplete or may hav been (partly) lost. Possibly some event during the early phase of the disease ("critica period") has effected the normal course of the vestibular compensation. It would be o value to find objective measures to show the difference between patients who do an those who do not recover well. The only finding in our study to this respect was tha less disabled patients tended to have a relatively good high-frequency VOR. Except fo one patient, we observed that patients with the best VOR gain at higher frequencie tend to perform better in daily life and considered themselves less disabled. Th possible role of the COR in the compensation proces in patients with bilateral vestibu lar impairment, was discussed earlier in this chapter.

The passive high-frequency head rotation test was shown abnormal in Meniere' disease patients and in patients with bilateral caloric hyporeflexia. This suggested relationship between vestibular function and the high-frequency VOR. As betahistin

is known to affect either vestibular function or reduce vestibular complaints, we studied the effect of betahistine upon the VOR in patients responding positively to betahistine. We observed that betahistine had no effect on the duration of nystagmus induced by low-frequency whole body rotation in the dark in Meniere's disease patients. Oosterveld reported a 50-60% decrease in duration of nystagmus activity at similar dosages of betahistine in a group of healthy volunteers.[39] Oosterveld stated that the effect of betahistine in normal subjects was normalized in such a way that, in our patient study, a maximum 5% decrease in nystagmus duration could be expected (personal communication). However, the sensitivity of our test is insufficient to detect such a small effect. The superior resolution reported by Oosterveld might be due to the fact that volunteers can be trained and instructed better than patients which improves reproducibility and reduces variability.
We found a maximum 20% decrease of the mean low-frequency VOR gain between 4 and 6 hours after administration of 16 mg betahistine. The effect of betahistine on high-frequency VOR gain was also unexpected, with a maximum decrease of up to 50% observed between 4 and 6 hours after administration of 32 mg betahistine. Lower or higher doses showed a less pronounced effect. A small, but not statistically significant, increase in VOR gain was observed in the first 2 hours after administration. Oosterveld reported a steady increase of the effect of betahistine upon nystagmus duration, up to a dose of 64 mg in healthy volunteers.[44] This does not agree with results obtained in our study with respect to the VOR gain.

Several factors may account for the complex effect of betahistine on the VOR gain. Firstly, as patients have functional disturbances of the system under investigation, any direct comparison with healthy volunteers must remain speculative. Secondly, a U-shape dosage effect relationship has also been found for the effect of neuron peptides upon the firing rate of neurons in the vestibular nucleus.[45]
The complex relationship between gain change and dosage in this study may be attributed to the complex histamine-receptor mechanisms involved. Histamine inhibits its own release at the H_3 autoreceptor, a process which can be antagonized by low concentrations of betahistine thereby facilitating histaminergic neurotransmission in the brain. However, at high concentrations of betahistine, the impact on the H_3 receptor system might be reversed or the H_1-agonistic activity may be invoked, thus cancelling the effect.
This study supported the hypothesis that betahistine acts upon the vestibular system in the subjective responser population. The high-frequency passive head rotation appeared to be a more accurate test to detect the effect of betahistine compared to low-frequency whole body rotation test.

Future perspectives

Testing the VOR at high frequencies is attractive because it reveals the physiological range of head movements, but also because contamination of the VOR by the visual ocular control system is generally considered small or absent in the high frequency range.

A fairly recent development in testing the VOR, is the combination of both active and passive high-frequency head rotation tests. The advantage of the active head rotation test is that no expensive rotatory device is necessary and that it can be applied at the bedside. The disadvantage in our hands was however, that most normal subjects were not able to reach rotation frequencies of over 4 Hz. Besides, active head rotation resulted in many non-harmonic sinusoidal components, which complicated analysis of the data. Our results clearly indicated that active or passive head rotation tests are not reliable if a simple head mounted angular rate sensor is used for detection of head velocity.

In this research project passive head rotation resulted in 6 Hz head rotation in all subjects and in a more sinusoidal stimulus, which simplified the analysis. In patiens with Meniere's disease and in patients with bilateral vestibular impairment the high-frequency head rotation test has proven to be a supplement to the standard vestibular tests routinely used in many clinics, such as caloric stimulation and the torsion swing test. However, in patient populations a large variability in results exist. For the time being we consider the passive high-frequency head rotation test designated for specialised vestibular centers. Small signals during high frequencies result in difficult signal analysis. We are still working to improve this aspect, so that the test will be broadly applicable.

The caloric stimulation test is the test mainly applied to distinguish left from right sided vestibular pathology. However, the stimulus is non-physiological and the test-retest variability is large. The high-frequency head rotation test as described in this thesis is not able to distinguish left from right sided vestibular pathology. Recent development shows promising results of tests using unpredictable high-velocity step displacements of the head.[5,6,46,47,48,49] The frequency spectrum of such head movements contains high frequencies. The VOR responses found using these tests were evidently *asymmetrical* in patients with unilateral vestibular loss, even 1 year after the vestibular lesion was induced. Using high-velocity step displacements of the head a lower gain and a prolonged delay of eye movements were found when moving the head towards the side of the lesion. The VOR delay is considered to be a potentially significant parameter of vestibular functionality. This means that the side of vestibular impair-

ment can be assessed even after compensation is completed, if physiological stimuli are applied (high-velocity step displacement of the head). So far, these tests have been using the magnetic search coil technique for detection of head and eye movements. In a pilot study we have tried to reproduce the findings using EOG, which is more patient friendly and easier applicable. However, the eye movements using unpredictable high-velocity impulses could not be detected properly using EOG. This clearly limits the clinical applicability of the impulse test, as the magnetic search coil technique is semi-invasive and blurs vision after 20 minutes and is therefore clinically not widely accepted. Further development of alternative eye position detecting techniques such as video-oculography might be useful in this respect.

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Chapter

8

Samenvatting

Inleiding

Een primaire functie van het evenwichtsorgaan is de hersenen te informeren over bewegingen van hoofd en lichaam en oriëntatie ten opzichte van de zwaartekracht. Hierdoor ontstaat een goede ruimtelijke oriëntatie en lichaamsstabiliteit. Bovendien is het evenwichtsorgaan het primaire systeem, dat zorgt voor de vestibulo-oculaire reflex (VOR). De VOR wordt in het algemeen veronderstelt het scherp zien te ondersteunen, door het genereren van oogbewegingen die gelijk zijn in snelheid en tegengesteld aan de richting van hoofdbewegingen. Hierdoor staan de ogen vrijwel stil in de ruimte terwijl het hoofd beweegt. Tijdens langzame hoofdbewegingen speelt het visuele systeem een grote rol bij de oogbewegingen, maar tijdens *snelle* hoofdbewegingen is het evenwichtsorgaan het enige systeem dat zorgt voor de blikstabilisatie. Dit heeft tot gevolg, dat men bijvoorbeeld tijdens lopen of autorijden op een hobbelige weg toch verkeersborden goed kan blijven lezen. De VOR is het belangrijkste thema van onderzoek in dit proefschrift.

De meest gebruikte "fysiologische" test waarbij de VOR opgewekt en gekwantificeert wordt om een indruk te krijgen over de functie van het evenwichtsorgaan, is de draaistoeltest, waarbij het hele lichaam van de proefpersoon wordt rondgedraaid. Gezien de technische beperkingen van de meeste draaistoelen gebeurt dit vrijwel altijd bij lage frequenties (< 1 Hz). Als het al mogelijk was om de stoel sneller te laten draaien, zou het erg moeilijk zijn om hoofd en lichaam goed aan de stoel te fixeren.
Het draaistoelonderzoek gebeurt in het donker, om zo de invloed van het visuele systeem te beperken. Juist hierdoor zijn de resultaten van het draaistoelonderzoek erg variabel en afhankelijk van de instructies die worden gegeven en de alertheid van de proefpersoon.

Willen we op andere wijze de "zuivere" VOR meten, zonder dat de blikstabilisatie door het visuele systeem beinvloed kan worden, dan zullen we de reflex moeten meten tijdens hoge frequenties waar het visuele systeem te traag is om de oogbewegingen te kunnen beinvloeden. Hiertoe zijn vrij recent zowel aktieve als passieve hoog-frequente hoofdrotatietesten ontwikkeld. Met als bijkomend voordeel dat geen dure draaistoel nodig zou zijn.

De parameters om de VOR te kwantificeren zijn de gain, fase en coherentie. De *gain* is gedefinieerd als het quotient van oogsnelheid (V_{oog}) en hoofdsnelheid (V_{hoofd}). De optimale gain (V_{oog}/V_{hoofd}) bedraagt 1, zodat oog- en hoofdsnelheid gelijk zijn en het beeld van de omgeving op het netvlies stilstaat. De *fase* is gedefinieerd als het tijdsverloop tussen oogsnelheid en hoofdsnelheid gerelateerd aan de frequentie (het faseverschil wordt aangegeven in graden). Een optimale fase bedraagt nul graden,

zodat er geen vertraging in de beeldstabilisatie is. De *coherentie* is gedefinieerd als de vormgelijkheid van tussen oog- en hoofdsnelheid en informeert ons derhalve over de kwaliteit van de signaalregistratie en de validiteit van de data; een ideale coherentie is 1. Oogbewegingen in dit onderzoek zijn gemeten door middel van Electro-Oculografie (EOG). De hoofdsnelheid werd gemeten door een hoeksnelheidsmeter op een hoofdband en later op een biteboard.

Doel van het onderzoek

Het doel van dit onderzoek was het ontwikkelen, verbeteren en evalueren van testen om de VOR te kwantificeren tijdens hoog-frequente hoofdrotatie.

Hoofdstuk 1

In de algemene inleiding wordt ingegaan op de achtergronden van het onderzoek. Kort wordt de fysiologie van de VOR besproken en uitgebreid wordt ingegaan op de functie van de VOR. De onderzoeksopzet wordt kort weergegeven. In een pilot studie hebben we een vergelijking gemaakt tussen het meten van de oogbewegingen door middel van EOG en met magnetische inductie spoeltjes (scleral coil technique (SCT)). EOG is een methode met electrodes rond het oog. De SCT is een methode, waarbij spoeltjes op het hoornvlies van het oog worden geplaatst na verdoving. We hebben geconcludeerd, dat EOG een betrouwbare methode is om oogbewegingen te meten tot circa 4-5 Hz; de methode is patiënt-vriendelijk en makkelijk toepasbaar in de kliniek.

Hoofdstuk 2

De hoog-frequente *aktieve* hoofdrotatietest wordt ook wel de Vestibulaire Autorotatie Test (VAT) genoemd. Hierbij wordt de proefpersoon gevraagd het hoofd van links naar rechts te bewegen op geleide van een klik met toenemende herhalingsfrequentie (2-6 Hz). In dit hoofdstuk wordt de methode uitgebreid besproken.
10 Normale proefpersonen werden onderzocht, waarbij de hoofdsnelheid werd gemeten met de snelheidsmeter op een hoofdband. We hadden de indruk, dat door beweging van de hoofdband ten opzichte van het hoofd bij hoge rotatiefrequenties, onnauwkeurigheden ontstonden in de detectie van de hoofdsnelheid. Hierop werden 2 proefpersonen onderzocht met zowel een snelheidsmeter op een hoofdband als op een biteboard. Het bleek dat de gain werd onderschat en de fase werd overschat in de eerste groep bij gebruik van de hoofdband. Dit werd bevestigd in een groep van 21

proefpersonen met een biteboard. In deze groep bleef de gain 1 en de fase 0^0 tot 6 Hz. In tegenstelling tot de literatuur bleek een aanzienlijk percentage van de gezonde proefpersonen niet in staat aktieve schudbewegingen te maken met een frequentie hoger dan 4 Hz.
Conclusie: door middel van de VAT kan de VOR op een reproduceerbare wijze worden gemeten in de hoge frequenties tot circa 4 Hz. mits de hoofdsnelheid wordt gedetecteerd met een biteboard.

Hoofdstuk 3

Aangezien tijdens aktieve rotatie veel normale proefpersonen niet in staat bleken het hoofd aktief in hoge frequenties te roteren, werd gestart met een *passieve* hoog-frequente hoofdrotatie test. Hierbij werd het hoofd passief geroteerd van 2-6 Hz. door middel van een computer gestuurde helm met motor naar het idee van prof. Collewijn uit Rotterdam. In dit hoofdstuk werd een vergelijking gemaakt tussen aktieve hoofdrotatie en passieve hoofdrotatie bij 14 gezonde proefpersonen. Tijdens de passieve hoofdrotatie bereikte iedereen zonder problemen 6 Hz. De gain en fase bleven tijdens aktieve rotatie optimaal, echter tijdens passieve rotatie daalde de gain tot 0.82 bij 6 Hz., de fase bleef wel optimaal 0^o. In dit hoofdstuk wordt in de discussie uitgebreid ingegaan op de mogelijke oorzaak van het verschil tussen aktieve en passieve hoofdrotatie en het verschil tussen hoofdrotatie en rotatie van het hele lichaam.

Hoofdstuk 4

M. Menière wordt in het algemeen beschouwd als een ziekte van het binnenoor, welke resulteert in de klassieke trias van symptomen: aanvallen van vertigo, eenzijdig perceptief gehoorsverlies en tinnitus. Er bestaat een grote variabiliteit in de uitkomsten van de twee meest uitgevoerde vestibulaire testen bij M. Menière. 30-50 Procent van de patiënten met M. Menière heeft normale responsies bij de calorisatie en het draaistoelonderzoek. De uitkomsten van deze laag-frequente vestibulaire testen worden niet meer meegenomen in de meeste recente internationale classificatienormen (AAO-HNS 1995). Dit wetende zijn we begonnen om de hoog-frequente passieve hoofdrotatietest toe te passen bij 20 patiënten met M. Menière. Boven de 3 Hz. werd bij de patiënten een significant grotere fasenaloop gevonden in vergelijking met normale proefpersonen. Interessant was, dat bij 4 patiënten met een normale calorisatie en draaistoelonderzoek, een afwijkende VOR werd gevonden tijdens hoge frequenties. Tussen 3-4 Hz. was het discriminatieve vermogen van de hoogfrequente test het grootst.

Hoofdstuk 5

Uit de kliniek is bekend, dat patiënten na uitval van een evenwichtsorgaan een opvallend vermogen hebben om dit verlies te compenseren, zodat de klachten vaak meevallen zelfs bij een dubbelzijdig verlies. Het vaststellen van de vestibulaire restfunctie bij patiënten met een dubbelzijdige uitval is een probleem. Calorisatie wordt beschouwd als equivalent aan stimulatie met een lage frequentie, zodat men kan veronderstellen, dat de resultaten van hoog-frequente testen niet in alle gevallen overeenstemmen met de calorisatie. Meer specifiek; een calorische onprikkelbaarheid betekent nog niet vestibulaire uitval. In dit hoofdstuk werden de resultaten beschreven van de passieve hoog-frequente hoofdrotatietest bij 8 patiënten met een bilaterale calorische hypo- of areflexie. We vonden bij alle patiënten een substantiële VOR boven 2 Hz., maar de gain boven 4 Hz. was bij alle patiënten lager in vergelijking met normale proefpersonen. Een verkennende discriminant analyse toonde, dat de combinatie van de gain bij 4.5 Hz. en de gain bij het draaistoelonderzoek een goede correlatie bleek te hebben met de klachten van de patiënt. Resultaten van de calorisatie hadden in dit onderzoek geen toevoegende waarde met betekking tot de klachten van de patiënt.

Hoofdstuk 6

Betahistine wordt verondersteld de vestibulaire functie te beïnvloeden en zo klachten te doen verminderen. In dit hoofdstuk werd onderzocht of een hypothetische vestibulaire functieverandering door betahistine een verandering geeft in de responsies tijdens de hoog-frequente passieve hoofdrotatietest. Deze dubbel-blind placebo gecontrolleerde studie vond plaats bij 12 patiënten met paroxysmale vertigo, die baat meenden te hebben van betahistine. Direkt voor en 1,2,3,4,6 en 8 uur na intake van 16, 32 of 64 mg. betahistine, vond een draaistoelonderzoek plaats en tevens de hoog-frequente passieve hoofdrotatietest. Betahistine beïnvloedde de gain tijdens het laagfrequent draaistoelonderzoek, maar meer nog de gain tijdens de hoog-frequente hoofdrotatietest. Het efffect van betahistine was maximaal bij een gemiddelde dosis van 16-32 mg. Om de complexe dosis afhankelijkheid van het effect te verklaren werd verondersteld dat betahistine de neurotransmissie op meerdere plaatsen in de hersenen, waaronder in de vestibulaire kernen, gelijktijdig beinvloedt.